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The First Reaction of Dimethoxycarbene with an Imine

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The nucleophilic dimethoxycarbene (DMC) generated by thermal decomposition of 2,5-dihydro-1,3,4-oxadiazole derivatives **1** in boiling toluene reacts smoothly with *N*-(fluoren-9-ylidene)toluene-4-sulfonamide (**7b**) to yield an imidocarbonate derivative **10**. A multi-step reaction pathway, initiated by the attack of DMC onto the C,N bond and followed by the migration of the sulfinate anion is proposed to explain the formation of the final product. In contrast to ketimine **7b**, *N*-(benzylidene)toluene-4-sulfonamide (**7a**) does not react with DMC under comparable conditions.

Key words: Azomethine ylides, Aziridines, Carbenes, Imines, Imidocarbonates

1. Introduction. – Dimethoxycarbene (DMC) belongs to the class of nucleophilic carbenes. The first method for its generation, based on the thermal decomposition of a 7,7-dimethoxynorbornadiene derivative at 140°, was reported by *Hoffmann et al.* [1]. Another method, used by *Moss* and coworkers, is the thermal or photochemical decomposition of 3,3-dimethoxy-3*H*-diazirine, but it has not been used for preparative purposes [2]. The thermal decomposition of 2,5-dihydro-2,2-dimethoxy-5,5-dimethyl-1,3,4-oxadiazole (**1**), elaborated by *Warkentin* and coworkers [3][4], opened new perspectives for numerous synthetic applications of DMC as a versatile building block. In a recent paper, **1** was used for the generation of DMC in the gas-phase under FVP conditions, and subsequent analysis of the pyrolysate at 10 K enabled the conformational analysis of the carbene [5]. For practical applications of DMC, the introduction of the modified precursor, in which one Me group is replaced by a 4-methoxyphenyl residue, is of significant practical importance, because the decomposition can be carried out already at 50° [6].

In the chemistry of carbenes, the reactions with multiple bonds are of special importance [7]. The addition to C,C-double bonds, known as cyclopropanation reactions, are widely applied in the synthesis of complex molecules [8]. Reactions with hetero- π -systems are also extensively elaborated in order to prepare three-membered heterocycles (oxiranes, thiiranes, aziridines) or products resulting from the interception of the initially formed ylide species [7].

In the case of the nucleophilic dimethoxycarbene, the most extensively studied reactions with relevant practical applications (two- or multi-component reactions) are focused on the use of ketones [4][9] or mixtures of acetylene dicarboxylate and an aldehyde [10] as substrates. Recently, DMC was shown to react smoothly with cycloaliphatic thioketones [11]

and dithiocarboxylates [12]. Cyclopropanones, cyclobutanones, and cyclopentanone react with DMC to give ring enlarged products [9], whereas 9*H*-fluoren-9-one and cyclohexanone yield methyl α -hydroxycarboxylates *via* the initially formed oxiranes [13][14]. Analogous reactions with ‘cage’ ketones lead to the corresponding α -hydroxy esters [15]. The reactions of DMC with C,N-double bonds are limited to isocyanates, which occur *via* a zwitterionic intermediate **3**. In the case of unsaturated isocyanates with $R = CR^1=CHR^2$, subsequent 1,5-cyclization leads to pyrrolidones **4** (*Scheme 1*). This methodology has been widely applied for the preparation of a variety of natural products [16]. In addition, decomposition of **1** in the presence of aryl isocyanates in chlorobenzene was shown to yield tetramethoxy- β -lactams **5** in competition with the formation of isatin derivatives **6** [17].

Scheme 1

To the best of our knowledge, no reports on the reactions of DMC with aldimines or ketimines have been published to date. In a recent paper, we described that electron-deficient imines derived from hexafluoroacetone failed to react with DMC [18]. The present study is aimed at the examination of the reactivity of imines, which are activated by a sulfonyl group attached to the N-atom, toward DMC.

Formulae 7a and 7b

2. Results and Discussion. – For the study presented in this paper, *N*-tosylimines of benzaldehyde and 9*H*-fluoren-9-one, *i.e.* compounds **7a** and **7b**, were selected. Both

substrates are easily available by condensation of tosylamine with the corresponding carbonyl compound in the presence of NEt_3 and TiCl_4 [19].

The decomposition of **1** was carried out in the presence of **7** in boiling toluene under an Ar atmosphere. In both cases, the reaction was finished after 7 h, and the crude products were analyzed by ^1H -NMR spectroscopy. The imine **7a** failed to react with DMC, and the dimer of the latter was the main product containing MeO groups. It was identified by the chemical shift of four equal MeO groups (3.53 ppm), which fits well with the reported data [20]. Other minor products formed in this reaction underwent decomposition during the attempted separation on silica gel.

The TLC-analysis of the reaction mixture obtained with **7b** showed the absence of the starting imine, and the ^1H -NMR analysis revealed the presence of two equally intense MeO signals located at 3.10 and 4.00 ppm, and one Me signal at 2.33 ppm for the tolyl residue. These data suggested the formation of a new product corresponding to 1:1-stoichiometry of DMC and **7b**. After crystallization from hexane, yellowish crystals with a m.p. of 178–180° were obtained. The IR spectra (KBr) showed an intense absorption at 1663 cm^{-1} , and the presence of a C,N-double bond was confirmed by the ^{13}C -NMR spectrum with the characteristic signal at 161.8 ppm.

The spectroscopic evidence excluded the structure of an aziridine for the isolated product. The result obtained with **7b** should be compared with those described by *Pole* and *Warkentin* in the case of the reaction of DMC with 9*H*-fluoren-9-one, where the oxirane **8** was observed in the reaction mixture along with the rearranged product **9** [13] (*Scheme 2*). In the light of the data of the product isolated from the reaction with **7b**, the structure corresponding to **9** with $\text{X} = \text{NSO}_2\text{C}_6\text{H}_4\text{Me}(p)$ could be proposed. However, the X-ray crystal-

structure determination solved the problem, unambiguously disclosing the unexpected structure **10** (*Figure*).

Figure. *ORTEP-plot* [21] of the molecular structure of one of the three symmetry-independent molecules of **10** (50% probability ellipsoids, arbitrary numbering of atoms)

A mechanistic interpretation of the formation of **10** is presented in *Scheme 3*. Under the assumption that the nucleophilic DMC attacks the imino C-atom to form the zwitterion **11** in analogy to the reactions with carbonyl groups, ring closure to give the aziridine **12** is necessary to explain the further reaction pathway *via* the intermediate azomethine ylide **13**. The appearance of the latter is conclusive as the C,N-bond attached to the fluorenyl ring is preserved in the product **10**. However, this interpretation is not compatible with the observed lack of reactivity in the case of **7a**, which is believed to be more reactive toward nucleophilic reagents. Therefore, the attack of DMC at the N-atom of **7b**, leading directly to **13**, is a plausible alternative. Finally, a 1,2-sulfonyl migration leads to the isolated product **10**, but the release of sulfinate to form an ion pair, which recombines to yield **10**, cannot be excluded.

In conclusion, the formation of **10** as the sole product of the reaction of the imine **7b** with DMC indicates that the transient azomethine ylide **13** isomerizes via migration of the sulfinate group. The reaction pathway leading to **13** is not clear, but the intermediacy of aziridine **12** formed via **11** is doubtful. One of the arguments of this interpretation is that aziridines bearing electron-donating substituents at a C-atom and/or electron-withdrawing substituents at the N-atom are not suitable precursors for the thermal generation of

azomethine ylides [22]. Despite the mechanistic consideration, the presented results show that DMC can in principal react with an electron-deficient imine group. In contrast to the analogous reaction with an electron-deficient ethylene derivative [23], the expected [2+1]-cycloadduct has not been detected. Instead, isomeric products, resulting from further conversion of the intermediate aziridine or its precursor, are formed.

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Experimental Part

1. *General.* M.p.'s were determined in capillary using a *Meltemp 2* apparatus and are uncorrected. ^1H - and ^{13}C -NMR spectra were registered with a *Bruker 200* and *400* spectrometer, respectively (200 and 100 MHz, resp.) using TMS (= 0 ppm) as an internal standard. IR spectra were taken in KBr pellets with a *Nexus FT-IR* spectrophotometer. CI-MS were recorded on a *Finnigan-Mat-90* spectrometer. Elemental analyses were performed in the Analytical Laboratory of the University of Zürich.

2. *Starting materials.* 2,2-Dimethoxy-5,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (**1**) was prepared according to the procedure published by *Warkentin* and his collaborators [3]. The *N*-sulfonylated imines **7a** and **7b** were synthesized from tosyl amide and benzaldehyde (0°, CH₂Cl₂) or fluorenone (boiling CH₂Cl₂, Et₃N), respectively, in the presence of TiCl₄ and Et₃N: *N*-benzylidene-(4-methylbenzene)sulfonamide (**7a**), pale yellow crystals, m.p. 109–111° ([24]: 107°); *N*-fluoren-9-ylidene-(4-methylbenzene)sulfonamide (**7b**), orange-yellow crystals, m.p. 184–186° ([19]: 182–184°).

3. *Reaction of DMC with Imine 7b:* 1,2,4-Oxadiazole **1** (240 mg, 1.5 mmol) and imine **7b** (333 mg, 1.5 mmol) were dissolved in 3 ml of abs. toluene under Ar. The mixture was heated under reflux, and the progress of the reaction was monitored by TLC (SiO₂, CH₂Cl₂/hexane). After 4 h, imine **7b** was completely consumed, heating was stopped and the solvent was evaporated to dryness. The residual viscous oil was triturated with Et₂O, and after several min at r.t., pale yellow crystals were separated by filtration. An analytically pure sample of *dimethyl N*-[9-(toluene-4-sulfonyl)-9H-fluoren-9-yl]iminocarbonate (**10**) was obtained by crystallization from hexane: 289 mg (71%). Colorless crystals. M.p. 178–180° (hexane). IR (KBr): 1664_{vs} (C=N), 1463_m, 1451_m, 1300_s, 1143_s, 1090_m, 752_m, 670_m, 580_m. ¹H-NMR (200 MHz): 7.49, 7.01 (AA'BB', *J* = 8, 4 arom. H); 7.43–7.15 (*m*, 8 arom. H); 3.99, 3.11 (2_s, 2 MeO); 2.33 (*s*, Me). ¹³C-NMR (100 MHz): 153.2 (*s*, C=N); 143.7, 141.5, 132.4 (3_s, 6 arom. C); 131.1, 129.8, 127.7, 127.1, 125.6, 119.6 (6_d, 12 arom. CH); 90.1 (*s*, (MeO)₂C); 56.5, 54.9 (2_q, 2 MeO); 21.6 (*q*, Me). CI-MS (NH₃): 257 (22), 254 (18), 240 (18), 238 (100, [*M*-C₇H₇NO₂S]⁺). Anal. calc. for C₂₃H₂₁NO₄S (407.49): C 67.79, H 5.19, N 3.44, S 7.87; found C 67.88, H 5.08, N 3.26, S 7.60.

4. *Attempted Reaction of DMC with Imine 7a*: 1,2,4-Oxadiazole **1** (240 mg, 1.5 mmol) and imine **7a** (389 mg, 1.5 mmol) were dissolved in 3 m of abs. toluene under Ar, and the mixture was heated under reflux as in the previous case. After 4 h, the evolution of N₂ was finished indicating complete decomposition of **1**; heating was stopped and the solvent was evaporated. The semi-solid residue was analyzed by ¹H-NMR spectroscopy; the spectrum showed significant amounts of the imine **1a** along with some unidentified products in low yield.

5. *X-Ray Crystal-Structure Determination of 10* (Figure)¹). All measurements were performed on a *Nonius KappaCCD* area-detector diffractometer [25] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream 700* cooler. The data collection and refinement parameters are given below and a view of the molecule is shown in the Figure. Data reduction was performed with *HKL Denzo* and *Scalepack* [26]. The intensities were corrected for *Lorentz* and polarization effects, and an absorption correction based on the multi-scan method [27] was applied. The structure was solved by direct methods using *SHELXS97* [28], which revealed the positions of all non-H-atoms. There are three symmetry-independent molecules in the asymmetric unit. The atomic coordinates of the three molecules were tested carefully for a relationship from a higher symmetry space group using the program *PLATON* [29], but none could be found. The non-H-atoms were refined anisotropically. All of the H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed

¹) CCDC-638213 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the *Cambridge Crystallographic Data Center* via http://www.ccdc.cam.ac.uk/data_request/cif.

isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom ($1.5U_{eq}$ for the Me groups). The refinement of the structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\sum w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied. Five reflections, whose intensities were considered to be extreme outliers, were omitted from the final refinement. Neutral atom scattering factors for non-H-atoms were taken from [30], and the scattering factors for H-atoms were taken from [31]. Anomalous dispersion effects were included in F_c [32]; the values for f' and f'' were those of [33]. The values of the mass attenuation coefficients are those of [34]. All calculations were performed using the SHELXL97 program [35].

Crystal data for 10: $C_{23}H_{21}NO_4S$, $M = 407.47$, colorless, prism, crystal dimensions $0.25 \times 0.25 \times 0.30$ mm, monoclinic, space group $P2_1/n$, $Z = 12$, $a = 9.2447(2)$ Å, $b = 18.0563(4)$ Å, $c = 37.0577(8)$ Å, $\beta = 90.7056(8)^\circ$, $V = 6185.4(2)$ Å³, $D_X = 1.313$ g·cm⁻³, $\mu(MoK\alpha) = 0.186$ mm⁻¹, $T = 160$ K, ϕ and ω scans, transmission factors (min; max) 0.859; 0.958, $2\theta_{max} = 60^\circ$, total reflections measured 139999, symmetry independent reflections 18076, reflections with $I > 2\sigma(I)$ 8878, reflections used in refinement 18071, parameters refined 794, R (on F ; $I > 2\sigma(I)$ reflections) = 0.0596, $wR(F^2)$ (all reflections) = 0.1653 ($w = (\sigma^2(F_o^2) + (0.0759P)^2)^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$), goodness of fit 1.011, secondary extinction coefficient 0.0037(4), final Δ_{max}/σ 0.001, $\Delta\rho$ (max; min) = 0.43; -0.51 e Å⁻³.

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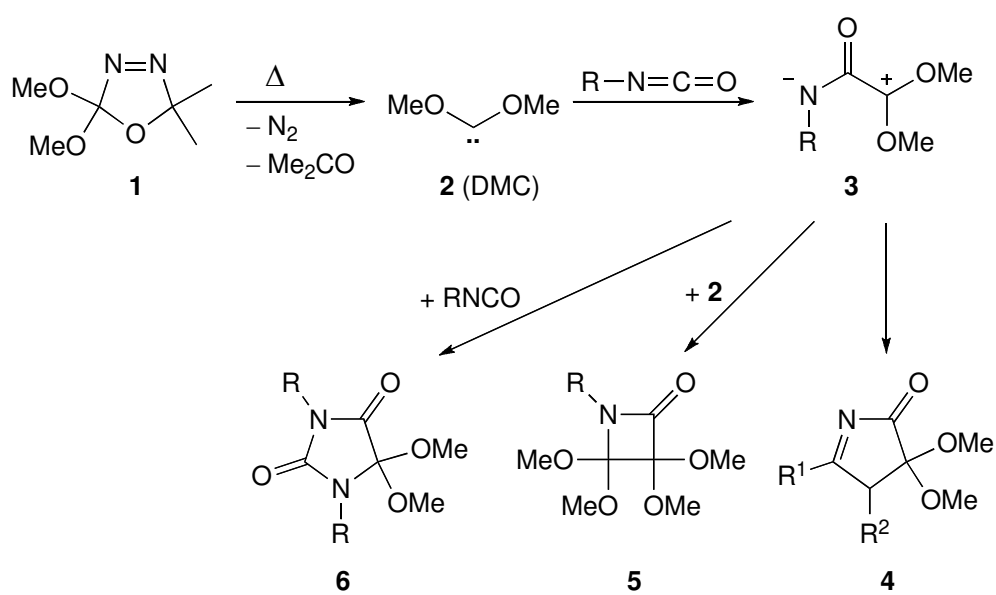
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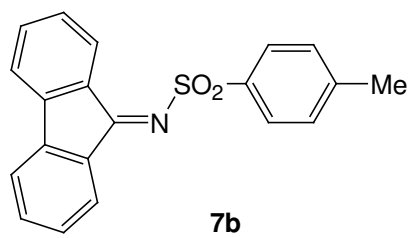
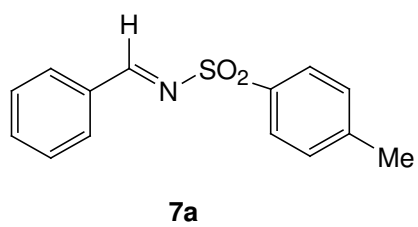
Legend

Figure. *ORTEP-plot* [21] of the molecular structure of one of the three symmetry-independent molecules of **10** (50% probability ellipsoids, arbitrary numbering of atoms)

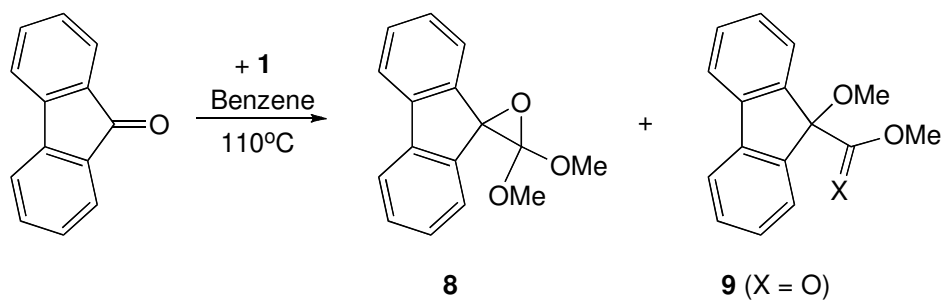
Scheme 1



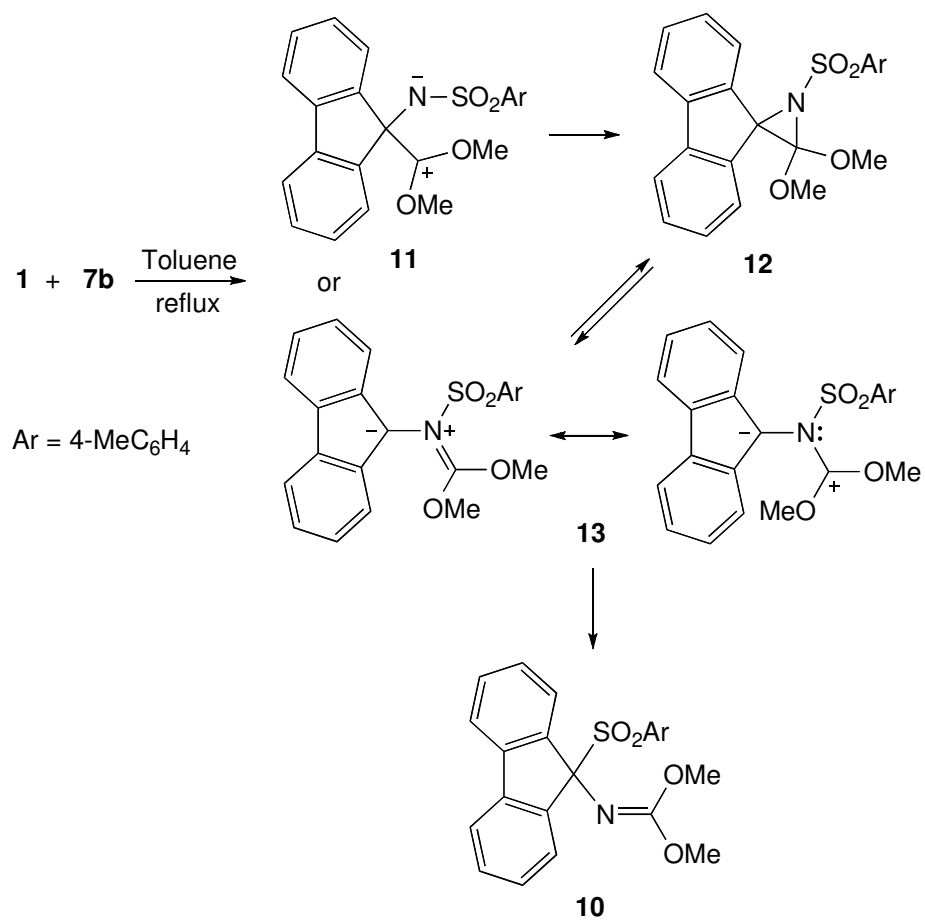
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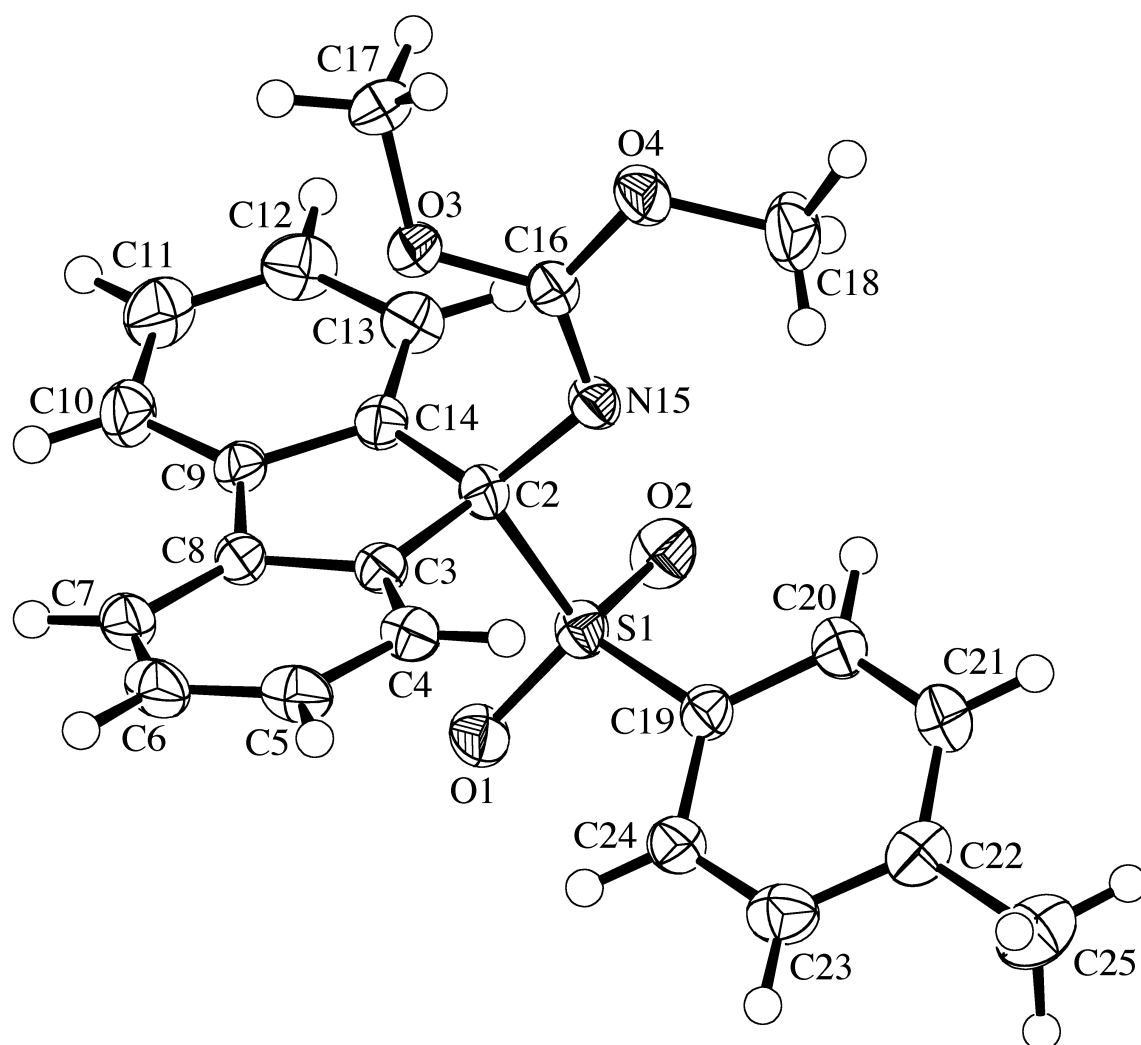


Scheme 2



Scheme 3



Figure

Graphical Abstract